

corrections made in the substitute pages are discussed below. None of the changes are deemed to constitute new matter.

#### SUMMARY OF THE INVENTION

The present invention is directed to a novel class of retroviral vectors that have been engineered to be capable of transducing mammalian cells at such high efficiency that no selection step is required (when used with the appropriate packaging cells lines). Given that no selection is required, the presently described retroviral vectors do not encode a functional selectable marker. This feature of the present vectors renders them novel over all prior art retroviral vectors, and provides the additional advantage that present vectors may incorporate larger inserted genes than previous retroviral vectors.

#### REMARKS

##### **I. Provisional Double Patenting Rejections**

The Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 5, 6, and 15 under 35 U.S.C. §§ 101 and 102(e) over U.S. application Ser. No. 07/786,015, now abandoned.

The Applicants request that the Examiner postpone further consideration of the provisional obviousness-type rejection of claims 1 through 4 and 6 through 8 over U.S. application Ser. No. 08/486,858 until claims in either application have been deemed allowable.

## II. Rejections based on prior art.

### A. Rejections under 35 U.S.C. § 103 in view Cone and Mulligan in conjunction with Temin and Bender et al.

The Examiner has rejected Claims 1-4, 6-8, 20, 21, and 35-37 as obvious over the teaching of Temin in view of Bender et al. (Bender) and Cone and Mulligan (Cone). The Examiner's rejection of the claims based on 35 U.S.C. § 103 over the combined teaching of Temin, Bender, and Cone is respectfully traversed. Neither Temin nor Bender teach or suggest recombinant retroviral vectors that are capable of transducing mammalian cells without selection. Accordingly, Temin and Bender cannot be combined to teach recombinant retroviral vectors which lack a complete selectable marker.

Cone is ostensibly cited because it contains a comment that titers of  $>10^5$  virus per ml are high enough to enable the nonselective introduction of genes into 100% of a population of cells. However, Cone merely suggested that titers of approximately  $10^5$  virus per ml were "...high enough to facilitate the nonselective introduction of genes into 100% of a population of cells...". In fact, such titers are woefully inadequate for the stated purpose as evidenced by the fact that the Examiner has cited no prior art references teaching retroviral transduction without selection.

Where the prior art, as a whole, does not explicitly suggest the claimed invention, a proper obviousness analysis under §103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would have also revealed that in so

carrying out, those of ordinary skill would have a reasonable expectation of success, *In re Vaeck*, 947 F.2d 488, 493 (Fed.Cir.1991). Thus, given Cone's "suggestion", a proper *prima facie* obviousness rejection requires that the Examiner establish that the teaching provided by the combined references would have provided a reasonable expectation of success. However, in spite of the fact that seven years had elapsed between Cone's alleged suggestion, and the effective filing date of the present application, the Examiner has cited no references that affirmatively demonstrate the construction and operability of retroviral vectors that lack a selectable marker. In other words, the Examiner has provided no evidence supporting the reasonable expectation of success.

One of the legally recognized considerations of nonobviousness is the "failure of others" to construct the claimed invention (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, (Fed. Cir. 1986)). The Examiner is respectfully requested to consider that the level of ordinary skill in the art is very high in the field of biotechnology, and that the pace of innovation is equally impressive. The Applicants submit that the absence of any reference teaching the successful implementation of Cone's allegedly enabling suggestion during the seven years prior to the effective filing date of the present application constitutes clear and convincing evidence that the claimed invention is *per se* nonobvious over the art of record. In fact, the demonstrated "failure of others" is compelling evidence of nonobviousness that effectively rebuts the alleged *prima facie* case of obviousness raised by the Examiner.

In view of the Applicants' clear rebuttal of the Examiner's *prima facie* case of obviousness, it is incumbent upon the Examiner to present evidence that the teaching of Cone would have provided a reasonable expectation of successfully constructing and practicing the claimed retroviral vectors. Presently, the Examiner has provided no evidence that the cited art of record would have provided one of ordinary skill with a reasonable expectation of success. Lacking such evidence, the Examiner has not established the legal basis for a proper obviousness rejection. Accordingly, the Examiner is respectfully requested to reconsider and withdraw rejections under 35 U.S.C. § 103 over the teaching of Cone.

As further support of the above position, the Applicants are submitting herewith the Declaration of Dr. Lawrence Cohen. In his Declaration Dr. Cohen states that it is his expert opinion that the concentrations of retrovirus disclosed by Cone would have not provided one of ordinary skill with a reasonable expectation of successfully transduce mammalian cells without selection. Dr. Cohen provides supporting evidence for his opinion in the form of personal statements, and a reference which shows that one must generally use a concentration of retrovirus that is at least about an order of magnitude higher than that taught by Cone in order to practice efficient transduction without selection.

In brief, Dr. Cohen's Declaration provides additional proof that Cone's unsupported and conclusory statement was wrong. Accordingly, the Examiner's reliance on Cone is also wrong. Given that an inoperative combination can not provide

one of ordinary skill with teaching sufficient to provide a reasonable expectation of success, the Applicants respectfully request that the Examiner further reconsider and withdraw the rejection of the pending claims as obvious over Cone.

The Examiner is also respectfully requested to consider that, especially where the transduced mammalian cells are to be used *in vivo*, it is generally desirable to minimize the cell's expression of foreign gene products. For example, the neo gene product is derived from a bacterial transposon, and is thus foreign to the body. Given that the presence of foreign proteins in the body may be expected to elicit an immune response against the transduced cells, it is clear that many *in vivo* applications of transduced cells mitigate against the presence and expression of a selectable marker. None of the cited prior art even mention this problem, and thus it is impossible for the Examiner to now argue that the cited references somehow teach or suggest the solution. In fact, in view of the above considerations, it should be clear that references teaching retroviral vectors that incorporate and express a functional selectable marker actually teach away from the invention as presently claimed.

Case law clearly holds that non-obviousness can lie in the discovery of a problem, the solution to which employs the combination of old elements, see, *In re Spinnoble*, 160 U.S.P.Q. 237 (CCPA 1969). Moreover, the non-obviousness involved in the discovery of the reason for the problem can impart patentability to the solution thereto, even though by hindsight the cause of the problem once recognized may suggest the solution. *In re Leonnart and Espy*, 135 U.S.P.Q. 307 (CCPA

1962), *Trio Process Corp. v. L. Goldsteins Sons, Inc.*, 174 U.S.P.Q. 129 (CA3 1972), *In re Roberts et al.*, 176 U.S.P.Q. 313 (CCPA 1973), *In re Nomiya et al.*, 184 U.S.P.Q. 607 (CCPA 1975), *Ex parte Campbell et al.*, 211 U.S.P.Q. 575 (POBA 1980). Additionally, the Examiner is directed to *In re Peehs and Hunner*, 204 U.S.P.Q. 835 (CCPA 1980), where the Court stated:

Where the Applicant contends that the discovery of the source of a problem would have been unobvious [non-obvious] to one of ordinary skill in the pertinent art at the time the claimed invention was made, it is incumbent upon the PTO to explain its reasons if it disagrees. A mere conclusionary statement that the source of a problem would have been discovered is inadequate. As this court explained in *In re Sponnoble*, 56 CCPA 823, 832, 405 F.2d 578, 585, 160 USPQ 237, 243 (1969): "A patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103."

Simply put, none of the cited publications, alone or in combination, explicitly suggest that it may be desirable to construct retroviral vectors which do not encode complete selectable markers. Thus, it is axiomatic that since none of the cited references even recognized the problem, the references, alone or in combination, could not have motivated or suggested the solution to one of ordinary skill in the art. Absent such motivation or suggestion, the cited art cannot properly support a *prima facie* case of obviousness under 35 U.S.C. § 103.

Given the above perspective, the Applicants respectfully submit that the presently claimed vectors (which do not encode or express a complete selectable marker) are *per se* nonobvious, and, accordingly, the Examiner is respectfully

requested to withdraw the rejections of claims 2-6, 9-20, and 22-31 under 35 U.S.C. § 103.

The Examiner has also rejected claims 2-4 and 20 as unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Temin, Cone, and Bender. The Applicants respectfully traverse the rejection for the reasons stated above regarding the inadequacies of the Cone reference.

The Examiner has also rejected claims 9 and 20 as unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Temin, and Cone, in further view of Kenten *et al.* (Kenten), or Kuo *et al.* (Kuo). The Applicants note neither Kenten nor Kuo teach or suggest retroviral vectors that lack selectable markers. Thus, the teaching of Cone is central to the Examiner's rejection, and the Applicants respectfully traverse the rejection for the reasons stated above regarding the inadequacies of the Cone reference.

The Examiner has also rejected claims 10, 11, 17, 18, and 20 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, and Cone, in further view of Emerman *et al.* (Emerman). Since Emerman does not teach or suggest the construction or use of retroviral vectors that lack a selectable marker, the teaching of Cone is also the centerpiece of this rejection. The Applicants respectfully traverse the rejection for the reasons stated above.

The Examiner has also rejected claims 16 and 20 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, and Cone, in further view of Emerman, and Yee *et al.* (Yee) or Yu *et al.* (Yu). Since none of Yee, Yu, or Emerman teach or suggest the construction or use of retroviral vectors

that lack a selectable marker, the teaching of Cone remains key to this rejection. Given that the teaching of Cone is inoperative, the Applicants respectfully traverse the rejection for the reasons stated above.

The Examiner has also rejected claim 19 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, and Cone, in further view of Emerman, Yee, or Yu. Since none of Yee, Yu, or Emerman teach or suggest the construction or use of retroviral vectors that lack a selectable marker, the teaching of Cone is apparently the hub of this rejection. Given that the teaching of Cone is inoperative, the Applicants respectfully traverse the rejection for the reasons stated above.

The Examiner has also rejected claims 12-15, 20 and 22 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, Cone, and Emerman in further view of Anderson and deVilliers. As discussed above, none of Temin, Emerman, Anderson, or deVilliers teach or suggest the construction or use of, or even a motivation for, retroviral vectors that do not encode a functional selectable marker. Accordingly, the Examiner is respectfully requested to withdraw this rejection in view of the previously discussed inadequacies of the teaching of Cone.

The Examiner has also rejected claims 23 and 24 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, Cone, Anderson, and deVilliers in further view of Hilberg et al. (Hilberg) or Holland et al. (Holland). None of Temin, Anderson, deVilliers, Hilberg, or Holland teach or suggest the construction or use of, or even a motivation for,



retroviral vectors that do not encode a functional selectable marker. Accordingly, the Examiner is respectfully requested to withdraw this rejection in view of the previously discussed inadequacies of the teaching of Cone.

The Examiner has also rejected claims 25-31 as obvious under 35 U.S.C. § 103 over the combined teachings of Temin, Cone, Anderson, and deVilliers taken with Hilberg or Holland, or in further view of Franz *et al.* (Franz). None of Temin, Anderson, deVilliers, Hilberg, Holland, or Franz teach or suggest the construction of, use of, or even a motivation for, retroviral vectors that do not encode a functional selectable marker. Accordingly, the Examiner is respectfully requested to withdraw this rejection in view of the previously discussed inadequacies of the teaching of Cone.

### **III. Rejections under 35 U.S.C. § 112**

The Examiner has rejected claims 1-31 and 35-37 because of certain objections to the specification for failing to provide an adequate written description of the invention. In particular, the Examiner has cited the specification at page 10, lines 27-28 where a typographical error resulted in several unlabeled boxes which correspond to regions of Fig. 11.

As requested by the Examiner, the Applicants are submitting substitute pages 10 and 11 that contain the corrections requested by the Examiner. In particular, the shading corresponding to the ADA cDNA (which is clearly labeled in Fig. 11(A)); and the shaded regions corresponding to MPSV and Friend sequences (which are also clearly and

unambiguously shown in Fig. 11(A), e.g., "MPSV-LTR"). Further support for the shaded MPSV sequence may be found at page 10, lines 12-16 where the specification describes the 385 bp *Nhe I-Sac I* fragment containing the MPSV enhancer that is clearly marked in Fig. 11(A) (note: the "*Nhe I-Sac I*" fragment of MPSV DNA shown in the "MPSV-Enh" construct). Similarly, support for the shaded regions corresponding to Friend sequences are clearly and unambiguously shown in Fig. 11(A) and are described in the specification at page 10, lines 22-25 (note: the "*Nhe I-Kpn I*" fragment (of Friend sequence from pFr-SV) that is clearly marked in Fig. 11(A). The applicants have also removed the empty boxes ("□") from substitute page 10, at line 34, and substitute page 11, at line 1 because of the specification's description of an ADA expressing variant of  $\alpha$ -SGC is deemed to be self-explanatory (especially in view of the detailed structure of  $\alpha$ -SGC presented in Fig. 4 and the clearly shaded region of ADA sequence shown in Fig. 11). While preparing substitute page 11, the Applicants also corrected the following typographical errors:

- 1) Line 10, "copy" was replaced with --copies--.
- 2) Line 12, "correspond" was replaced with --corresponding--.
- 3) Line 27, "activity control" was replaced with --activity. Control--.

In view of the above comments, the corrected pages are not deemed to constitute new matter. In view of the above corrections to the specification, the Examiner's rejection of claims 1-31 and 35-37 under 35 U.S.C. § 112, first paragraph is deemed to have been avoided by amendment.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe that the application is in good and proper condition for allowance. Early notification to that effect is earnestly solicited. If the Examiner feels that a telephone call would expedite the consideration of the application, the Examiner is invited to call the undersigned attorney at (415) 926-7405. The Commissioner is authorized to charge any underpayment or credit any overpayment to the deposit account number 16-1150 for any matter in connection with this response, including any fee for extension of time which may be required.

Respectfully submitted,

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